EFFICACY OF DOTS IN CHILDHOOD TUBERCULOSIS USING PAEDIATRIC PATIENT-WISE BOXES

Dissertation submitted to

THE TAMILNADU

DR. M.G.R MEDICAL UNIVERSITY, CHENNAI

With Partial fulfillment of the regulations

For the award of the Degree of

MD BRANCH VII

PAEDIATRIC MEDICINE

GOVT. KILPAUK MEDICAL COLLEGE & HOSPITAL
CHENNAI

THE TAMILNADU DR. MG.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

MARCH 2010

CERTIFICATE

Certified that this dissertation entitled "**EFFICACY OF DOTS IN CHILDHOOD TUBERCULOSIS USING PAEDIATRIC PATIENT-WISE BOXES"** is a bonafide work done by **Dr. ARUN KUMAR SUBRAMANIAN,** Post graduate student of Paediatric Medicine, Kilpauk Medical College Hospital, Chennai-10, during the academic year 2007-2010.

Prof. Dr. M. Kannaki, M.D.,D.C.H.,
Professor and Head of the Dept,
Department of Paediatrics,
Kilpauk Medical College Hospital,
Chennai – 10

Prof. Dr. V. Kanagasabai M.D.,
Dean,
Kilpauk Medical College Hospital,
Chennai - 10

DECLARATION

I declare that this dissertation entitled "**EFFICACY OF DOTS IN CHILDHOOD TUBERCULOSIS USING PAEDIATRIC PATIENT-WISE BOXES"** has been conducted by me at Kilpauk Medical College Hospital. It is submitted in part of fulfilment of the award of the degree of M.D (Paediatrics) for the March 2010 examination to be held under **The Tamilnadu DR.M.G.R Medical University, Chennai.** This has not been submitted previously by me for the award of any degree or diploma from any other university.

ACKNOWLEDGEMENT

I express my sincere thanks to **Prof. V. Kanagasabai M.D., Dean**, Kilpauk Medical College, for allowing me to conduct this study using the available facilities.

I am greatly indebted to **Prof. Dr. M. Kannaki, MD., D.C.H.,** Professor and Head of the Department of Paediatrics, Kilpauk Medical College Hospital, who was my guide for the dissertation. I thank her wholeheartedly for her able guidance and encouragement throughout the study.

I am immensely grateful to **Prof. Dr. L. Uma Devi MD., D.C.H.,** Former Professor and Head of the Department of Paediatrics, Kipauk Medical College Hospital, for her support and encouragement as well as suggestions given for my study.

I would like to express my sincere thanks to **Dr. M. S. Mani MD.,** Assistant Professor, Department of Paediatrics, Kilpauk Medical College Hospital, for his valuable suggestions which have been incorporated in this dissertation.

I am indebted to **Dr.Mahali MD., DCH.,** Addl Professor, Department of Paediatrics Kilpauk Medical College Hospital and Professor

Dr. V. Seetha MD., former Professor, Department of Paediatrics, Government Royapettah hospital and Professor **Dr. D. Guna Singh MD., D.C.H.,** Professor of Paediatrics, Government Royapettah Hospital.

I would like to thank the Assistant Professors of the Department of Paediatrics at Kilpauk Medical College Hospital, **Dr.M.Suganya MD., DCH., Dr.N.Balakrishnan MD., Dr.G.Srinivasan MD., Dr.A.Senthil Vadivu, MD.,** and **Dr.Meenakshi MD.** My sincere thanks also to **Dr. P. G. Raja Kumar MD.,** former Assistant Professor, Kilpauk Medical College Hospital.

I also extend my sincere thanks to the departments of Pathology, Biochemistry, Microbiology, Thoracic medicine KMCH & all the health care professionals involved in RNTCP and the statistician for their valuable support throughout my dissertation work.

I also thank my parents, my colleagues, friends and staff of our hospital, for their support.

CONTENTS

INTRODUCTION

It is estimated that about one third of the world's population is infected with *Mycobacterium tuberculosis* [1]. Not all people infected have the disease, and most of them are adults. Tuberculosis (TB), however, remains an under-diagnosed and neglected entity in children. A total of 8.3 million new cases of TB were reported worldwide in 2000, of which an estimated 11% cases were children and the reported percentage of all TB cases occurring in children varied from 3% to more than 25% in different countries.[2,3]

Infection with *M. tuberculosis* usually results from inhalation into the lungs of infected droplets produced by someone who has pulmonary TB and who is coughing. The source of infection of most children is an infectious adult in their close environment (usually the household). This exposure leads to the development of a primary parenchymal lesion (Ghon focus) in the lung with spread to the regional lymph node(s). The immune response (delayed hypersensitivity and cellular immunity develops about 4–6 weeks after the primary infection. In most cases, the immune response stops the multiplication of *M.tuberculosis* bacilli at this stage. However, a few dormant bacilli may persist. A positive tuberculin skin test (TST) would be the only evidence of infection.

.

Progression of disease occurs by: (i) extension of the primary focus with or without cavitation, (ii) the effects of pathological processes caused by the enlarging lymph nodes, or (iii) lymphatic and/or haematogenous spread. Children who develop disease usually do so within 2 years following exposure and infection, i.e. they develop primary TB. A small proportion of children with TB (generally older children) develop post-primary TB either due to reactivation, after a latent period, of dormant bacilli acquired from a primary infection or by reinfection.

The Revised National Tuberculosis Control Programme (RNTCP)[6], which was initiated in 1997, included the treatment of pediatric cases according to body weight. The regimen recommended for treating the pediatric cases had been 2R3H3Z3 / 4R3H3 for children less than 6 years of age. For all children above 6 years, the same regimen was recommended as for adults.

In early 2004, in consultation with Indian Academy of Pediatrics, the recommendations were revised whereby Ethambutol was included for treatment of pediatric cases even under 6 years of age.The Programme had been getting feedback in regard to the difficulty in administering the drugs to smaller children as the available formulations needed to be broken up to meet the patients' individual weights.

.

To overcome these problems, RNTCP in consultation with IAP, has taken steps to make the pediatric drugs available in patient-wise boxes (PWBs) similar to those supplied for adult patients under RNTCP. With the availability of pediatric PWBs, all new pediatric patients diagnosed and registered for treatment under RNTCP, would be initiated on pediatric patient wise boxes. This will enable optimum dosage for the patients, without resorting to further breaking of the tablets,as per the respective weight bands.

.

ETIOPATHOGENESIS

ETIOLOGY

There are 5 closely related mycobacteria in the M. tuberculosis complex: M. tuberculosis, M. bovis, M. africanum, M. microti, and M. canetti. M. tuberculosis is the most important cause of tuberculosis disease in humans. The tubercle bacilli are non-spore-forming, nonmotile, pleomorphic, weakly gram-positive curved rods 2–4 μm long. They may appear beaded or clumped in stained clinical specimens or culture media.[8]

They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Loewenstein-Jensen culture media). These mycobacteria grow best at 37–41°C, produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is acid fastness—the capacity to form stable mycolate complexes with arylmethane dyes such as crystal violet, carbolfuchsin, auramine, and rhodamine. Once stained, they resist decoloration with ethanol and hydrochloric or other acids[12].

TRANSMISSION

Transmission of M. tuberculosis is person to person, usually by airborne mucus droplet nuclei, particles 1–5 μm in diameter that contain M.

.

tuberculosis. Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has an acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Environmental factors, especially poor air circulation, enhance transmission.

Most adults no longer transmit the organism within several days to 2 weeks after beginning adequate chemotherapy, but some patients remain infectious for many weeks. Young children with tuberculosis are rarely infectious. Tubercle bacilli are sparse in the endobronchial secretions of children with pulmonary tuberculosis, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. However, children and adolescents with adult-type cavitary or endobronchial pulmonary tuberculosis can transmit the organism[39].

PATHOGENESIS

The primary complex of tuberculosis includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts where most are killed, but some survive within nonactivated macrophages, which carry them through lymphatic

.

vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus may drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2–12 wk as the organisms grow in number and tissue hypersensitivity develops.

The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation. Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. Intense caseation results in cavity formation.

Despite fibrosis and encapsulation in the infected regional lymph nodes, viable M. tuberculosis can persist for decades within these foci. In most cases of initial tuberculosis infection the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction may encroach on a regional bronchus, resulting in hyperinflation in the distal lung segmentdue to partial obstruction or atelectasis due to complete obstruction. Inflamed caseous nodes can erode through bronchial walls, causing endobronchial tuberculosis or a fistula tract. The combination of pneumonitis and atelectasis, has been called a collapse-consolidation or segmental lesion.

.

LYMPH NODE DISEASE

Tuberculosis of the superficial lymph nodes, often referred to as scrofula, is the most common form of extrapulmonary tuberculosis in children. Historically, scrofula was usually caused by drinking unpasteurized cow's milk laden with M. bovis. Most current cases occur within 6–9 mo of initial infection by M. tuberculosis, although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen.. Systemic signs and symptoms other than a low-grade fever are usually absent. The tuberculin skin test is usually reactive, but the chest radiograph is normal in 70% of cases. The onset of illness is occasionally more acute, with rapid enlargement of lymph nodes, high fever, tenderness, and fluctuance.

Tuberculous lymphadenitis can usually be diagnosed by fine-needle aspiration of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size for months or even years. Surgical removal is not always necessary, and must be combined with antituberculous medication because the lymph node disease is but one part of a systemic infection.

.

DIAGNOSIS OF TB IN CHILDREN

The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. TST, chest X-ray (CXR) and sputum smear microscopy. Most children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible, e.g. by sputum microscopy for children with suspected pulmonary TB who are old enough to produce a sputum sample. [3]

RECOMMENDED APPROACH FOR DIAGNOSIS OF TB IN CHILDREN

1. **Careful history** (including history of TB contact and symptoms consistent with TB). The following points concerning contact are of importance for diagnosing TB in children.
   - All children aged 0–4 years and children aged 5 years and above who are symptomatic, who have been in close contact with a smear-positive TB case, must be screened for TB.
   - When any child (aged less than 15 years) is diagnosed with TB, an effort should be made to detect the source case (usually an adult with sputum smear-positive pulmonary TB) and any other undiagnosed cases in the household.

- If a child presents with infectious TB, child contacts must be sought and screened, as for any smear-positive source case. Children should be regarded as infectious if they have sputum smear-positive pulmonary TB or cavitary TB on CXR.

b. Symptoms.

In most cases, children with symptomatic TB develop chronic symptoms. The commonest are:

- Chronic cough

An unremitting cough that is not improving and has been present for more than 21 days.

- Fever

Body temperature of >38 °C for 14 days, after common causes such as malaria or pneumoniahave been excluded.

- Weight loss or failure to thrive

In addition to asking about weight loss or failure to thrive, it is necessary to look at the child's growth chart.

The specificity of symptoms for the diagnosis of TB depends on how strict the definitions of the symptoms are.

.

2. Clinical examination (including growth assessment)

There are no specific features on clinical examination that can confirm that the presenting illness is due to pulmonary TB. Some signs, although uncommon, are highly suggestive of extrapulmonary TB (i.e. TB of organs other than the lungs). Other signs are common and should prompt an investigation into the possibility of childhood TB.

Documented weight loss or failure to gain weight, especially after being treated in a nutritional rehabilitation programme, is a good indicator of chronic disease in children, of which TB may be the cause.

3. Tuberculin skin test

A positive TST occurs when a person is infected with M. tuberculosis, but does not necessarily indicate disease. However, the TST can also be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and when used in conjunction with other diagnostic tests. There are a number of TSTs available, but the TST using the Mantoux method is the recommended test.

4. Bacteriological confirmation whenever possible

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available. Appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture (and

.

also histopathological examination). Appropriate clinical samples include sputum, gastric aspirates and certain other material (e.g. lymph node biopsy or any other material that is biopsied). Fine-needle aspiration of enlarged lymph glands – for both staining of acid-fast bacilli and histology – has been shown to be a useful investigation, with a high bacteriological yield. In addition to increasing the yield of confirmed TB cases, mycobacterial culture is the only way to differentiate M. tuberculosis from other nontuberculous mycobacteria.

Common ways of obtaining samples for smear microscopy include the following.

a. Expectoration

Sputum should always be obtained in adults and older children (10 years of age or older) who are pulmonary TB suspects. Among younger children, especially children under 5 years of age, sputum is difficult to obtain and most children are sputum smear-negative. However, in children who are able to produce a specimen, it is worth sending it for smear microscopy (and mycobacterial culture if available). Bacterial yields are higher in older children (more than 5 years of age) and adolescents, and in children of all ages with severe disease. As with adult TB suspects, three sputum specimens should be obtained: an on-the-spot specimen (at first

.

evaluation), an early morning specimen and a second on-the-spot specimen (at a follow-up visit).

b. Gastric aspiration

Gastric aspiration using a nasogastric feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. Gastric aspirates should be sent for smear microscopy and mycobacterial culture. A gastric aspirate should be obtained on each of three consecutive mornings.

c. Sputum induction

Several recent studies have found that sputum induction is safe and effective in children of all ages and the bacterial yields are as good as or better than for gastric aspirates. However, training and specialized equipment are required to perform this procedure properly.

In developing and improving laboratory services for TB diagnosis, the priority is to ensure there is a network of quality controlled microscopy laboratories for staining acid-fast bacilli in clinical samples, most often sputum.

5. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

a. Suspected pulmonary TB

.

Chest radiography is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. The commonest picture is that of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB. Patients with persistent opacification which does not improve after a course of antibiotics should be investigated for TB. Adolescent patients with TB have CXR changes similar to adult patients with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation.

Adolescents may also develop primary disease with hilar adenopathy and collapse lesions visible on CXR. Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a health-care worker trained in their reading. A practical guide for interpreting CXRs has been developed.

b. Suspected extrapulmonary TB

In most of these cases, TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

.

Common forms of extrapulmonary TB in children

Site	Practical approach to diagnosis
Peripheral lymph nodes (esp. cervical)	Lymph node biopsy or Fine needle aspiration
Miliary TB (e.g. disseminated)	Chest X-ray and lumbar puncture (to test for meningitis)
TB meningitis	Lumbar puncture (and computerized tomography)
Pleural effusion	Chest X-ray, pleural tap for (older children and adolescents) biochemical analysis (protein & glucose concentrations) cell count and culture
Abdominal TB	Abdominal ultrasound and ascitic tap (e.g. peritoneal)

Standard case definitions of TB in children

The diagnosis of TB refers to the recognition of an active case, i.e. a patient with symptomatic disease (due to M. tuberculosis infection). Beyond the diagnosis of TB disease, the type of TB case should also be defined to enable appropriate treatment to be given and the outcome of treatment evaluated. The case definition is determined by the: (i) site of disease, (ii) result of any bacteriological tests, (iii) severity of TB disease, and (iv) history of previous anti-TB treatment. All children with TB should be registered with the RNTCP as smear-positive pulmonary, smear-negative pulmonary TB or extrapulmonary TB, and as a new case or a previously treated case. Standard case definitions are provided below

.

Pulmonary TB, sputum smear-positive

The criteria are:

- two or more initial sputum smear examinations positive for acid-fast bacilli; **or**
- one sputum smear examination positive for acid-fast bacilli plus CXR abnormalities consistent with active pulmonary TB, as determined by a clinician; **or**
- one sputum smear examination positive for acid-fast bacilli plus sputum culture positive for *M.tuberculosis*.

Adolescents, or children of any age with complicated intrathoracic disease, are more likely to have sputum smear-positive pulmonary TB.

Pulmonary TB, sputum smear-negative

A case of pulmonary TB that does not meet the above definition for smear-positive pulmonary TB. Such cases include cases without smear results, which should be exceptional in adults but relatively more frequent in children. In keeping with good clinical and public health practice, diagnostic criteria for sputum smear-negative pulmonary TB should include:

- at least three sputum specimens negative for acid-fast bacilli; **and**
- radiological abnormalities consistent with active pulmonary TB; **and**
- no response to a course of broad-spectrum antibiotics; **and**

.

- decision by a clinician to treat with a full course of anti-TB chemotherapy.

Extrapulmonary TB

Children with only extrapulmonary TB should be classified under this case definition. Children who have both pulmonary and extrapulmonary TB should be classified under the case definition of pulmonary TB.

Anti-TB treatment in children

Background

The main objectives of anti-TB treatment are to:

1. Cure the patient of TB (by rapidly eliminating most of the bacilli);
2. Prevent death from active TB or its late effects;
3. Prevent relapse of TB (by eliminating the dormant bacilli);
4. Prevent the development of drug resistance (by using a combination of drugs);
5. Decrease TB transmission to others.

Children usually have paucibacillary pulmonary disease (low organism numbers), as cavitating disease is relatively rare (about 6% of cases or fewer) in those under 13 years of age (the majority of the organisms in adult-type disease are found in the cavities). In contrast, children develop extrapulmonary TB more often than adults do. Severe and disseminated TB

.

(e.g. TB meningitis and miliary TB) occur especially in young children (less than 3 years old). Both the bacillary load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are generally good, even in young and immunocompromised children who are at higher risk of disease progression and disseminated disease, provided that treatment starts promptly. There is a low risk of adverse events associated with use of the recommended treatment regimens

Recommended treatment regimens

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated

.

Management of Pediatric Tuberculosis Under the Revised National Tuberculosis Control Programme

DOTS is the recommended strategy for treatment of TB and all Pediatric TB and all Pediatric TB patients should be registered under RNTCP[22,37].

Category of treatment	Type of patients	TB treatment regime	
		Intensive Phase	Continuation Phase
Category I	• New sputum smear positive PTB • Seriously ill sputum smear negative PTB with extensive parenchymal involvement (acute military, segmental/ lobar opacity) • Seriously ill extra-pulmonary TB includes disseminated/ military TB, TB pericarditis, TB peritonitis and intestinal TB, bilateral or extensive pleurisy, genitor-urinary tract TB, bone and joint TB.	2H3R3Z3E3	4H3R3
Category I	• CNS TB (meningitis, tuberculoma of brain, spinal TB with or without neurological complications and other part of nervous system)	2H3R3Z3S3	6-7H3R3

Category II	• Sputum smear-positive relapse, (with evidence of tubercular features) • Sputum smear-positive treatment failure, (with evidence of tubercular features) • Sputum smear-positive treatment after default, (with evidence of tubercular features)	2S3H3R3Z3E3/ 1 H3R3Z3E3	5 H3R3E3
Category III	• Sputum smear-negative and Extra-pulmonary TB, not seriously ill (TB adenitis, mediastinal lymphadenopathy, skin TB and not seriously ill abdominal TB)	2H3R3Z3	4H3R3

.

REVIEW OF LITERATURE

The literature review was done to understand the current status of clinical profile of tuberculosis in children, the treatment outcome and adverse effects associated with short course chemotherapy.

Age distribution

Vimlesh seth et al[24] has shown that age distribution was equal in all age groups except during infancy when it was rare.

Ileana Puiu et al[16] has shown that Tubercular lymphadenitis is more common in age group of 10 to 16 (39.1%) followed by 6 to 10 (25.2%)

Polesky [20] and co study shows that TB adenitis is more common in age group 10 to19

Sex distribution

Vimlesh seth et al [24] study shows that sex ratio indicates a male preponderance with male to female in the ratio of 1.5: 1 (67 : 46).

Ileana Puiu et al[16] has shown that the distribution of the cases according to sex reveals a slight predominance of females (51.6%), as compared to males (48.4%)

.

Jhaa et al[19] study has shown a slight female preponderance 1:1.3

Dandapat et al[18] has also shown a slight female preponderance 1:1.2

Castro et al[17] study also found a female preponderance 1:1.3.

Mantoux positivity

A study conducted at ICH Chennai Vijayasekaran et al [35] has shown that the positivity of Mantoux in lymph node tuberculosis (53%)

A study conducted at AIIMS by Vimlesh seth et al [24] shows that Mantoux test was positive in 96 (85%) children

Ileana Puiu et al [16] study has shown a 87.3% mantoux positivity.

Jhaa et al[19] also shows a higher mantoux positivity at 95%.

Dandapat et al[18] study shows that mantoux positivity is seen in 94%.

In Castro et al [17]study mantoux positivity is 74%.

Malnutrition

Vimlesh seth et al [24] study has shown that malnutrition is present in 88% of patients.

Balaji et al [36] study conducted at ICH Madurai has shown a significant correlation of malnutrition with TB adenitis

Contact history

.

A study conducted at ICH Chennai by Vijayasekaran et al [35]has shown that contact positivity is seen in 30.4% of patients.

A study conducted at AIIMS by Vimlesh seth et al [24] has shown a positive contact history in 19% of children.

Ileana Puiu et al [16] study has a positive contact history in 87.3% of children.

Radiological changes

Ileana Puiu et al[16] study has abnormal radiological findings in 21.8% of TB adenitis patients.

Jhaa et al[19] study shows abnormal radiological features in 16% of children with TB adenitis.

Polesky et al [20] study has shown abnormal radiological feature in 38% of children with TB adenitis.

Dandapat et al [18] 35% of children with TB adenitis had abnormal radiological findings.

Castro et al [17] study has abnormal radiological finding in 18% of children with TB adenitis.

Anemia

Ileana Puiu et al [16] study has shown anemia in 55.2% of children with TB adenitis.

.

Adverse symptoms

Al Dossary et al [25] has shown that adverse events are seen in 1.2 % of children on DOTS.

Te Water Naude et al[40] study has shown that none of the children had adverse events with DOTS.

In Tsakilidis D, et al [41] study none of the child had any adverse events taking DOTS.

Treatment outcome

CK Indumathi et al [42] study conducted at St.John's Medical College Hospital Bangalore has shown a overall cure rate of 95% including 97% cure rate in extra pulmonary TB and 94 % in pulmonary TB

Biddulph J et al [26] study has 7 relapse cases out of 373 cases

Gocmen A, et al [43] has 1 relapse case out of 130 cases

Tsakilidis D, et al [41] had no cases of relapse out of 36 children with TB

Guidelines for use of Pediatric Patient Wise boxes under the Revised National Tuberculosis Control Programme

The new formulations to be used in RNTCP are:

- Rifampicin – 75 /150 mg
- Isoniazid – 75 /150 mg

.

- Ethambutol – 200 /400 mg
- Pyrazinamide – 250 / 500 mg

For the purpose of treatment, the pediatric population is divided into four weight bands:

- 6 – 10 kgs
- 11 – 17 kgs
- 18 – 25 kgs
- 26 – 30 kgs

The anti–TB drugs for pediatric patients will be available in the form of 2 generic patient wise boxes i.e. Product Code 13 and Product Code 14. Product Code 15 and 16 would be available for the prolongation of the intensive phase, if required and also to facilitate conversion of the boxes into Category II and for reconstitution, if required.

The composition of product codes 13 to 16 is given below:

Product Code 13 - Treatment box for pediatric weight band category (6-10 Kg). Each treatment box containing 24 Combi-packs of Schedule5 in one pouch and 18 multi-blister calendar Combi-pack of Schedule-6 in another pouch.The intensive phase consists of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol to be given under direct observation thrice a week on alternate days for 2 months (24 doses).

.

The continuation phase consists of 4 months (18 weeks; 54 doses) of Isoniazid and Rifampicin given thrice a week on alternate days - the first dose of every weekly blister being directly observed.

Product Code 14 - Treatment box for pediatric weight band category (11-17 Kg). Each treatment box containing 24 Combi-packs of Schedule-7 in one pouch and 18 multi-blister calendar Combi-pack of Schedule-8 in another pouch.

The intensive phase consists of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol to be given under direct observation thrice a week on alternate days for 2 months (24 doses). The continuation phase consists of 4 months (18 weeks; 54 doses) of Isoniazid and Rifampicin given thrice a week on alternate days - the first dose of every weekly blister being directly observed.

Product Code 15 - Treatment box for prolongation of intensive phase of pediatric cases (6-10 kg and 18-25 kg). Each box containing 5 pouches and each pouch containing 12 blister Combi pack of Schedule-5.

The pouch consists of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol to be given under direct observation thrice a week on alternate days for 1 month (12 doses).

.

Product Code 16 - Treatment box for prolongation of intensive phase of pediatric cases (11-17 kg, 18-25 kg and 26-30 kg). Each box containing 5 pouches and each pouch containing 12 blister Combipacks of Schedule-7.Prolongation Pouch consists of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol to be given under direct observation thrice a week on alternate days for 1 month (12 doses).

The generic patient wise boxes, i.e. product code 13 and 14, according to weight band would be used for the pediatric patients in the following manner.

- A patient weighing 6 – 10 kg would require 1 box of Product Code 13.
- A patient weighing 11 – 17 kg would require 1 box of Product Code 14.
- A patient weighing 18 – 25 kg would require 1 box of Product Code 13 and 1 box of Product Code 14.
- A patient weighing 26 - 30 kg would require 2 boxes of Product Code 14.

The boxes have been designed to suit the requirements of Category I cases which are expected to dominate the patients belonging to pediatric age group. In case, any patients are to be placed on Category II or III, the following steps will have to be taken to convert the generic boxes into a Category II or III box:

.

Category II – Re-treatment Cases

For children to be placed on Category II, PPs would be added for prolongation of IP. For the extra 1 month of CP, a PP would be added after removing the Pyrazinamide tablets from the PP. For the other 4 months of CP blisters, Ethambutol tablets will need to be added which can be used from the supplies of loose drugs under the Programme.

SM Inj (750 mg) supplied under the programme shall be used for such patients and the dosage would be as per body weight.

Category III cases

For children who are to be put on Category III, the Ethambutol tablets will be removed from the IP blisters.

Categorization and duration of therapy

Categorization of pediatric cases will be as per RNTCP policy. The treatment regimens recommended under RNTCP are the same for adult and pediatric cases. The duration of therapy will be as per the treatment regimen. If required, the duration of therapy may be extended within the current RNTCP guidelines.

.

Use of Prolongation Pouches

Sputum positivity in the pediatric patients of lower weight categories is usually not found and it is also difficult to get a sputum sample in such children. However, for the older patients, sputum samples can be obtained and prolongation of intensive phase may be required. For such patients, prolongation pouches will be required. In addition, PP would also be required for the purpose of reconstitution of the PWBs of patients who have died, defaulted, transferred out and indoor patients who also would be treated under RNTCP using PPs.

Chemoprophylaxis

Asymptomatic children under 6 years of age, exposed to an adult with infectious (smearpositive) tuberculosis from within the same household, are to be given 6 months of Isoniazid (5 mg per kg daily) as chemoprophylaxis. Loose tablets of INH 100 mg would continue to be supplied for this purpose as was previously done.

OBJECTIVES OF THE STUDY

1. To assess the efficacy of DOTS using pediatric patient wise boxes under RNTCP in childhood tuberculosis- pulmonary and extra pulmonary (TB adenitis).

2. To study the adverse effects associated with these fixed drug formulations of patient wise boxes.

3. To study the clinical profile of TB adenitis in children.

.

METHODOLOGY

This study was undertaken in the pediatric department of Govt.Kilpauk Medical College Hospital during the period of January 2008 to june 2009. All the cases suspected to have tuberculosis are evaluated and if confirmed are registered in the TB clinic at Kilpauk Medical College.

The study was commenced after formal approval of the ethical committee of our hospital. The study population included all the pediatric inpatients and outpatients confirmed of pulmonary tuberculosis and TB lymphadenitis.

Inclusion Criteria:

All children upto 12 yrs of age diagnosed with pulmonary tuberculosis and TB adenitis.

Exclusion Criteria:

1. Other forms of extra pulmonary tuberculosis.
2. HIV infected children
3. Relapse, default and failure cases

.

Maneuver:

All children admitted in the pediatric department of Kilpauk Medical college hospital who are diagnosed to have pulmonary tuberculosis and those with TB adenitis are registered in TB clinic at Kilpauk Medical College Chennai and are enrolled in the study group from January 2008 to December 2008. These children are started on Anti-Tubercular drugs based on recent RNTCP guidelines using pediatric patient wise boxes. These children are then followed up for a period of six months.

All children who had signs and symptoms suggestive of tuberculosis are admitted in the pediatric ward. A detailed history was obtained. The history included the symptoms,duration, contact history, past history of tuberculosis, dietic history,immunization history especially BCG, and socioeconomic class.

A thorough clinical examination was done including the assessment of nutritional status. These children are subjected to the following investigations.

1. Complete blood count – hemoglobin, total count, differential count, ESR, and peripheral smear study.
2. Mantoux
3. X-ray chest

.

4. Sputum / RGJ for AFB
5. Liver function tests
6. Fine Needle Aspiration Cytology in patients with lymphadenitis.
7. HIV screening

The children are then diagnosed to have pulmonary tuberculosis based on WHO and RNTCP guidelines. They are then categorized according to the recent RNTCP guidelines. The Revised National Tuberculosis Control Programme (RNTCP), which was initiated in 1997, included the treatment of pediatric cases according to body weight. Until now, the same strategy has been continued. The regimen recommended for treating the pediatric cases had been 2R3H3Z3 / 4R3H3 for children less than 6 years of age. For all children above 6 years, the same regimen was recommended as for adults.

In early 2004, in consultation with Indian Academy of Pediatrics, the recommendations were revised whereby Ethambutol was included for treatment of pediatric cases even under 6 years of age. The Programme had been getting feedback in regard to the difficulty in administering the drugs to smaller children as the available formulations needed to be broken up to meet the patients' individual weights.

.

To overcome these problems, RNTCP in consultation with IAP, has taken steps to make the pediatric drugs available in patient-wise boxes (PWBs) similar to those supplied for adult patients under RNTCP. With the availability of pediatric PWBs, all new pediatric patients diagnosed and registered for treatment under RNTCP, would be initiated on pediatric patient wise boxes. This will enable optimum dosage for the patients, without resorting to further breaking of the tablets, as per the respective weight bands. Further, Rifampicin would be available in tablet form, which will enable easier swallowing of the drug by the pediatric patients.

In our study, these children are then followed up as per WHO guidelines. These children are followed up at 2,4,6 months of commencement of therapy. For those children who are sputum positive a repeat sputum was done on these occasions. For children who are diagnosed to have TB adenitis a repeat FNAC was done after 6 months. A decrease in size of the lymphnodes were also noted. A repeat X ray chest was taken for clearance of radiological changes after 6 months.

These children are monitored with serial measurement of weight and anthropometry. A repeat LFT and hemoglobin are done at the end of six months.

.

They are also enquired about the relief of symptoms,any adverse effects, school attendance,compliance, difficulty in procurement of these drugs.

The treatment was considered successful in children who became sputum negative, with >2/3 of clearance of radiological changes, with relief of symptoms and weight gain. For TB adenitis decrease in size and a normal FNAC finding in lymphnode was considered as successful treatment in the study.

All the statistical analysis was performed using the SPSS Software Version 10.0 package. Statistical tools such as chi-square test were used in the analysis. P-value of <0.005 is considered statistically significant.

.

RESULTS

112 children diagnosed with both pulmonary and TB adenitis were enrolled in the study, of which 82 cases were TB adenitis and 30 were pulmonary tuberculosis. The cases were registered in TB clinic and treatment started according to recent RNTCP guidelines using pediatric patient wise boxes. These children were the followed up for a period of 6 months. The treatment outcome and the adverse effects of the drug are then analysed.

Age distribution in TB adenitis

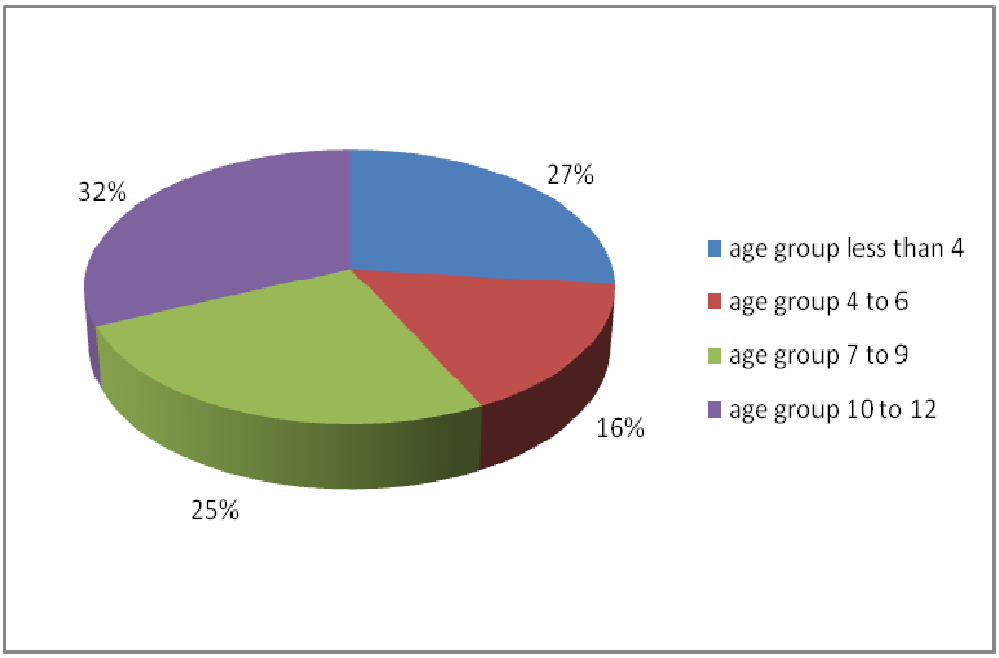
The age distribution of cases in this study group are

Age in yrs	Frequency	Percent	Valid Percent	Cumulative Percent
<3	22	26.8	26.8	26.8

.

3-6	13	15.9	15.9	42.7
7-9	21	25.6	25.6	68.3
10-12	26	31.7	31.7	100.0
Total	82	100.0	100.0	

AGE DISTRIBUTION



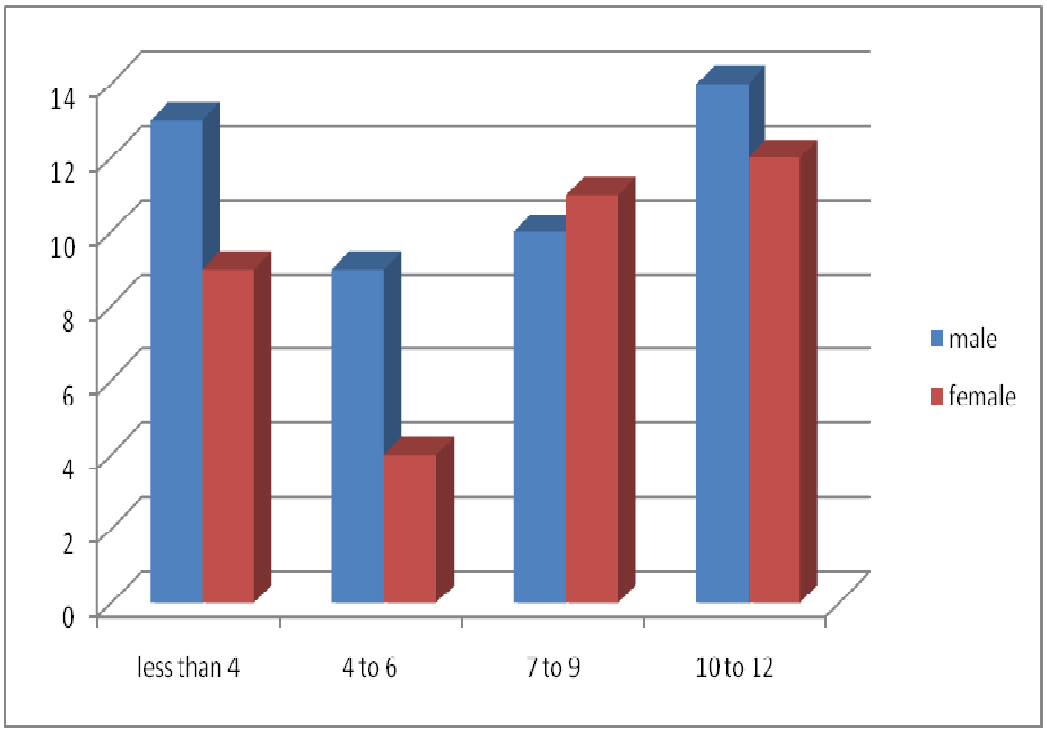
The prevalence of TB adenitis is more common in children aged more than 9 years (31.7%)

SEX DISTRIBUTION

Sex	Frequency	Percent	Valid Percent	Cumulative Percent
Female	36	43.9	43.9	43.9
male	46	56.1	56.1	100.0
Total	82	100.0	100.0	

There is a slight male preponderance in all age groups except for between 7 to 9 years as shown in the bar chart.

SEX DISTRIBUTION



MALNUTRITION

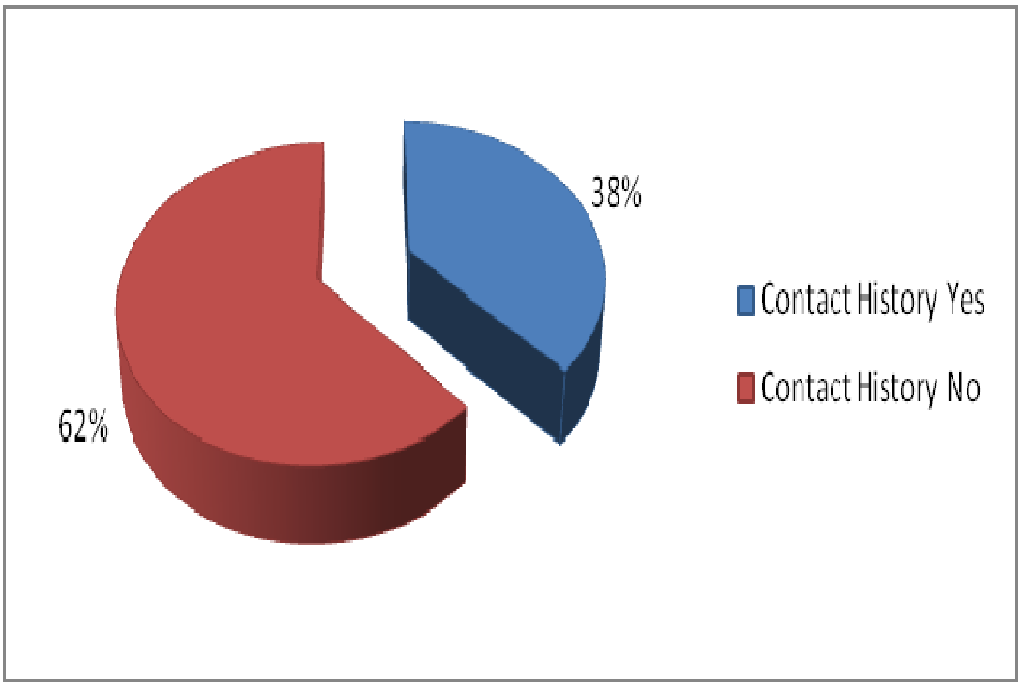
	Frequency	Percent	Valid Percent	Cumulative Percent
No	19	23.2	23.2	23.2
Yes	63	76.8	76.8	100.0
Total	82	100.0	100.0	

In this study out of the 82 children with TB adenitis 63 children 76.8% are undernourished.

CONTACT H/O

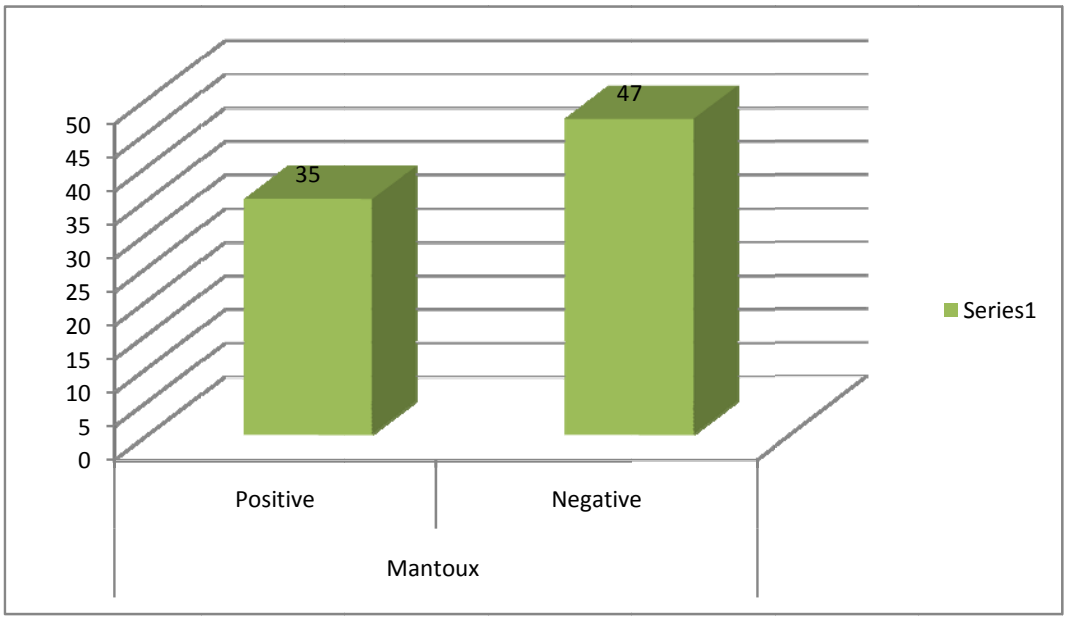
	Frequency	Percent	Valid Percent	Cumulative Percent
No	51	62.2	62.2	62.2
Yes	31	37.8	37.8	100.0
Total	82	100.0	100.0	

In our study a positive contact history is present in 31 cases (37.8%).



Mantoux Positivity

The mantoux is positive in 43% of children with TB adenitis

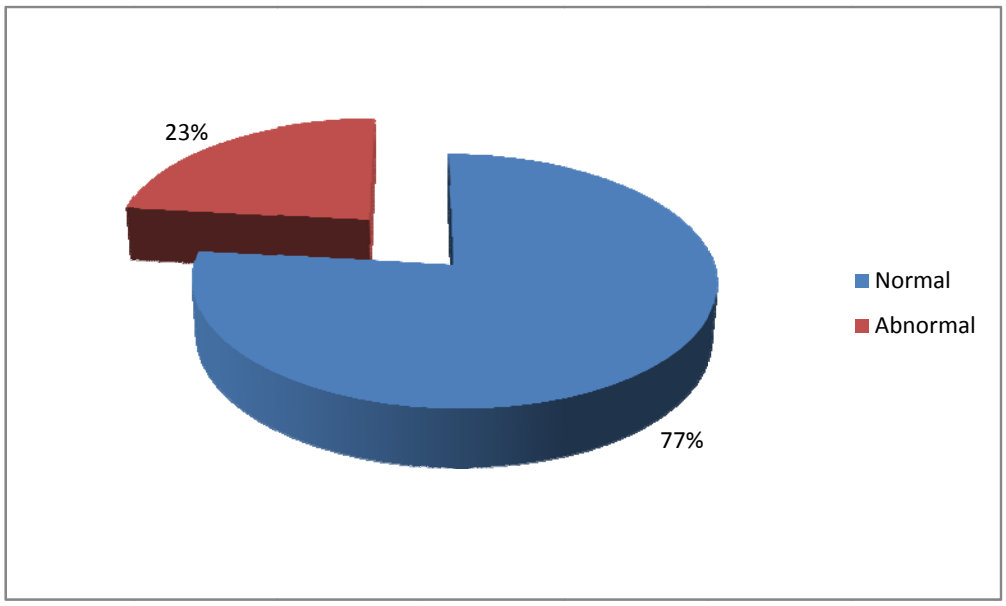


Radiological Changes

	Frequency	Percent	Valid Percent	Cumulative Percent
No	63	76.8	76.8	76.8
yes	19	23.2	23.2	100.0
Total	82	100.0	100.0	

The radiological changes are seen in 19 cases out of 82 cases which ia about 23.8% of cases of TB adenitis.

Radiological Changes

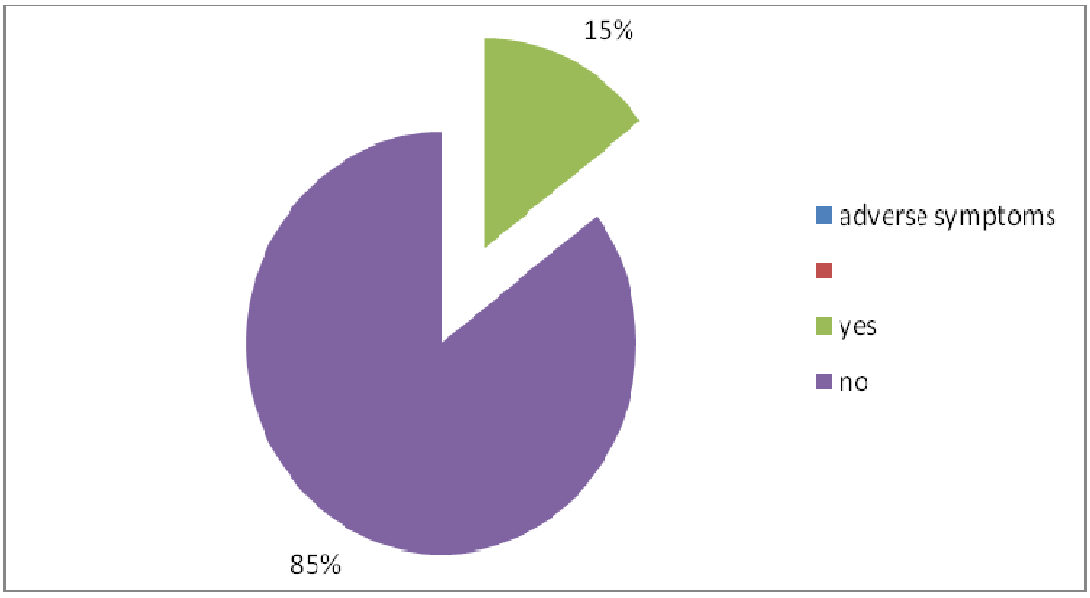


Adverse symptoms:

Of the 82 children on treatment with DOTS using pediatric patient wise boxes 12 had mild adverse effects in the form of nausea, vomiting which required only symptomatic management. None of the patients had serious adverse effects such as jaundice, visual defects.etc

ADVERSE SYMPTOMS

Adverse Symptoms	Frequency	Percent	Valid Percent	Cumulative Percent
No	70	85.4	85.4	85.4
Yes	12	14.6	14.6	100.0
Total	82	100.0	100.0	



The adverse symptoms in different age groups are tabulated

Crosstab

			ADVERSE SYMPTOMS		
			No	**Yes**	**Total**
AGE GROUP	Less than 4 yrs	Count	21	1	22
		% of Total	25.6%	1.2%	26.8%
	4 to 6 yrs	Count	12	1	13
		% of Total	14.6%	1.2%	15.9%
	7 to 9 yrs	Count	17	4	21
		% of Total	20.7%	4.9%	25.6%
	10 to 12 yrs	Count	20	6	26
		% of Total	24.4%	7.3%	31.7%
	Total	Count	70	12	82
		% of Total	85.4%	14.6%	100.0%

Chi square 4.105 p Value 0.250

This table shows that adverse symptoms are more common older age group children and younger children tolerate these drugs better than older ones.

.

Liver function test:

A baseline LFT was done before commencement of treatment which was normal in all the patients. A repeat LFT was done in all the patients during follow up.

LFT During Follow Up

Elevated	Frequency	Percent	Valid Percent	Cumulative Percent
No	75	91.5	91.5	91.5
yes	7	8.5	8.5	100.0
Total	82	100.0	100.0	

This table shows that LFT was elevated in 7 out of 82 cases. In all children there was only mild elevation of enzymes which did not require discontinuation of treatment. The serum bilirubin was normal in all the patients. LFT became normal after 2 months after the completion of treatment.

Treatment outcome:

Out of 82 children diagnosed with TB adenitis all are proved with features of granulomatous adenitis in FNAC. A decrease in size of the lymphnode is seen in all patients. A repeat FNAC was done to confirm the successful treatment outcome. The result are tabulated as follows.

FNAC 1 * FNAC 2 Crosstabulation

			FNAC 2		
			negative	positive	Total
FNAC 1	positive	Count	80	2	82
		% of Total	97.6%	2.4%	100.0%
	Total	Count	80	2	82
		% of Total	97.6%	2.4%	100.0%

The treatment was successful in 80 out 82 children. Only 2 children had persistent features of TB adenitis in the study group. An additional 3 months therapy was required in these children and an excision biopsy was done at the end of 9 months which did not show features of TB adenitis.

.

Radiological features:

The radiological features are present in 23.2% of cases. Following treatment there is resolution of features in all the children.

X RAY CHEST 1 * X RAY CHEST 2 Cross tabulation

			X RAY CHEST 2	
			Normal	**Total**
X RAY CHEST 1	Normal	Count	63	63
		% of Total	76.8%	76.8%
	Abnormal	Count	19	19
		% of Total	23.2%	23.2%
	Total	Count	82	82
		% of Total	100.0%	100.0%

Correlation of weight gain and hemoglobin with outcome:

All children enrolled in the study are monitored for weight gain during follow up. The hemoglobin level was also monitored. The levels at the end of treatment are correlated with the treatment outcome. The results are tabulated below.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	WEIGHT 1	17.9756	82	8.23869	.90981
	WEIGHT 2	20.9329	82	8.21838	.90757
Pair 2	Hb 1	10.7341	82	1.26961	.14020
	Hb 2	11.8073	82	1.01747	.11236

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	WEIGHT 1 & WEIGHT 2	82	.979	.000
Pair 2	Hb 1 & Hb 2	82	.819	.000

p value 0.000

In our study as shown above there is a strong positive correlation (.979),between weight gain and outcome. This table also shows a positive correlation (0.819) between rise in hemoglobin.

.

Paired Samples Test

		Paired Differences		
		Mean	**Std. Deviation**	**Std. Error Mean**
Pair 1	WEIGHT 1 - WEIGHT 2	-2.95732	1.67811	.18532
Pair 2	Hb 1 - Hb 2	-1.07317	.72946	.08056

Paired Samples Test

		Paired Differences				
		95% Confidence Interval of the Difference				
		Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	WEIGHT 1 - WEIGHT 2	-3.32604	-2.58860	-15.958	81	.000
Pair 2	Hb 1 - Hb 2	-1.23345	-.91289	-13.322	81	.000

Treatment outcome in pulmonary tuberculosis:

In our study, out of 30 cases diagnosed as pulmonary tuberculosis, 5 cases were sputum positive for AFB. All cases had abnormal radiological findings. Following treatment with category 1 of DOTS therapy using patient wise box , all the cases were cured at the end of therapy.

.

All sputum positive children became sputum negative for AFB at the end of Intensive therapy. Radiological resolution is confirmed at the end of six months therapy. There was clearance of x-ray findings in all the patients.

Correlation of treatment outcome with weight gain and hemoglobin in pulmonary tuberculosis:

A correlation between weight gain and rise in hemoglobin levels following treatment with outcome is assessed. The results are as follows.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	WEIGHT 1	16.87	30	7.181	1.311
	WEIGHT 2	18.93	30	7.353	1.342
Pair 2	Hb1	10.88	30	1.213	.222
	Hb2	11.95	30	.947	.173

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	WEIGHT 1 & WEIGHT 2	30	.992	.000
Pair 2	Hb1 & Hb2	30	.829	.000

The above table indicates that a positive correlation 0.992 with a p value of 0.000 between weight gain and treatment outcome is stastically significant.

Paired Samples Test

		Paired Differences		
		Mean	Std. Deviation	Std. Error Mean
Pair 1	WEIGHT 1 - WEIGHT 2	-2.067	.944	.172
Pair 2	Hb1 - Hb2	-1.073	.680	.124

.

Paired Samples Test

		Paired Differences				
		95% Confidence Interval of the Difference				
		Lower	**Upper**	**t**	**df**	**Sig. (2-tailed)**
Pair 1	WEIGHT 1 - WEIGHT 2	-2.419	-1.714	-11.986	29	.000
Pair 2	Hb1 - Hb2	-1.327	-.819	-8.643	29	.000

The paired t test also shows a significant p value 0.000

In our study during the follow up along with the nutritional assessment, all cases were enquired about the adverse symptoms, difficulty in drug procurement, compliance of the drug intake, school attendance in school going children.

In our study we found that there were no difficulty in drug procurement as they were directly observed by a health care professional, the compliance was also very good as the parents were repeatedly educated about the treatment. School attendance was not affected considerably except in cases of sputum positive children

.

DISCUSSION

It is estimated that about one third of the world's population is infected with *Mycobacterium tuberculosis* 1. Not all people infected have the disease, and most of them are adults. Tuberculosis (TB), however, remains an under-diagnosed and neglected entity in children. A total of 8.3 million new cases of TB were reported worldwide in 2000, of which an estimated 11% cases were children and the reported percentage of all TB cases occurring in children varied from 3% to more than 25% in different countries.

To combat this problem, The Revised National Tuberculosis Control Programme (RNTCP), which was initiated in 1997, included the treatment of pediatric cases according to body weight. The Programme had been getting feedback in regard to the difficulty in administering the drugs to smaller children as the available formulations needed to be broken up to meet the patients' individual weights. To overcome these problems, RNTCP in consultation with IAP, has taken steps to make the pediatric drugs available in patient-wise boxes (PWBs) similar to those supplied for adult patients under RNTCP.

Our aim of the study is to asses the treatment outcome of DOTS using patient wise boxes in childhood tuberculosis. Our study was done over a

.

period of one year from January 2008 to December 2008 and they are followed up for a period of six months and treatment outcome was assessed at the end of the study. The adverse effects associated with the drugs are also analysed. The clinical profile of TB adenitis was also analysed.

In our study, 112 cases were enrolled of which 82 were TB adenitis and 30 cases were pulmonary tuberculosis. Treatment was successful in 80 out of 82 cases of TB adenitis at the end of 6 months. Treatment was successful in all 30 cases of pulmonary tuberculosis.

All cases of TB adenitis were diagnosed by FNAC and a repeat FNAC was done at the end of six months. The pulmonary tuberculosis was diagnosed based on radiological changes and sputum positivity for AFB. Out of 30 cases of pulmonary tuberculosis 5 cases were sputum positive for AFB. The results are as follows.

In our study group TB adenitis was prevalent in all age groups and more common in children older than 9 years (31.7%). Vimlesh seth et al has shown that age distribution was equal in all age groups except during infancy when it was rare. Ileana Puiu et al has shown that Tubercular lymphadenitis is more common in age group of 10 to 16 (39.1%) followed by 6 to 10 (25.2%). Polesky and co study shows that TB adenitis is more common in age group 10 to19**.**

.

In our study the there is a slight male preponderance in children with TB adenitis (56%) with females (44%) and sex ratio of 1:3. Vimlesh seth et al study also document a male preponderance with male to female in the ratio of 1.5: 1 (67: 46).Ileana Puiu et al has shown that the distribution of the cases according to sex reveals a slight predominance of females (51.6%), as compared to males (48.4%). Jhaa et al, Dandapat et al, Castro et al studies also found a female preponderance.

The mantoux positivity rate in our study group with TB adenitis was 42.6%.A study conducted at ICH Chennai by Vijayasekaran et al has shown that the positivity of Mantoux in lymph node tuberculosis (53%). A study conducted at AIIMS by Vimlesh seth et al shows that Mantoux test was positive in 96 (85%) children. Ileana Puiu et al study has shown a 87.3% mantoux positivity .Jhaa et al also shows a higher mantoux positivity at 95%. Dandapat et al study shows that mantoux positivity is seen in 94%.In Castro et al study mantoux positivity is 74%.

Among 82 children with TB lymphadenitis malnutrition was seen in 63 children (76.8%). Vimlesh seth et al study has shown that malnutrition is present in 88% of patients Balaji et al study conducted at ICH Madurai has shown a significant correlation of malnutrition with TB adenitis.

.

A positive contact history was obtained in 31 cases (37.8%) out of 82 cases. A study conducted at ICH Chennai by Vijayasekaran et al., has shown that contact positivity is seen in 30.4% of patients and Vimlesh seth et al., study at AIIMS has shown a positive contact history in 19% of children. Ileana Puiu et al., study has a positive contact history in 87.3% of children. A low positive contact history indicates that there are still undetected cases of adult TB are prevalent in the community.

In our study, 19 out of 82 cases with TB adenitis had abnormal radiological changes in x-ray chest (23.2%). Ileana Puiu et al., study had abnormal radiological findings in 21.8%, Jhaa et al study 16%, Polesky et al study 38%, Dandapat et al 35%, Castro et al study 18% of children with TB adenitis.

Out of 82 cases who were started on either category 1 or 3 only 12 had mild adverse symptoms. 7 children had nausea and vomiting, 5 had only nausea. None of these children had severe adverse symptoms such as jaundice, visual defects, etc. Age distribution of adverse effects shows that these symptoms are less common in younger children. Out of 12 children 10 were above the age of 7 years. Al Dossary et al., has shown that adverse events are seen in 1.2 % of children on DOTS. Te Water Naude et al study has shown that none of the children had adverse events with DOTS. In

.

Tsakilidis D, et al study none of the child had any adverse events taking DOTS.

Liver function tests were also analysed before and during the treatment. In our study there was mild elevation of liver enzymes in 7 out of 82 children with TB adenitis and 1 out 30 cases in pulmonary tuberculosis. None of the children had elevation of serum bilirubin. All the cases with elevated LFT were followed up and none of them required discontinuation of treatment. The enzyme levels became normal in all patients one month after completion of treatment.

Treatment Outcome

In our study out of 82 children with TB adenitis, treatment was successful in 80 children. A repeat FNAC showed no evidence of tuberculosis in histopathological examination. In case of pulmonary tuberculosis out of 30 children treatment was successful in all the cases. Out of 30 children 5 were sputum positive for AFB. They became sputum negative at the end of intensive phase of therapy. Over all the cure rate was 98.2%. The cure rate was 97.5% with TB adenitis and 100% in children with pulmonary tuberculosis.

CK Indumathi et al study conducted at St.John's Medical College Hospital Bangalore has shown a overall cure rate of 95% including 97%

.

cure rate in extra pulmonary TB and 94 % in pulmonary TB. Biddulph J et al study has 7 relapse cases out of 373 cases Gocmen A, et al has 1 relapse case out of 130 cases Tsakilidis D, et al had no cases of relapse out of 36 children with TB.

A recent study by Joseph L Mathew[44] at PGI Chandigarh regarding the fixed dose combination therapy in childhood pulmonary tuberculosis. They concluded that there is no evidence of superiority of fixed-dose combination ATT over separate administration in terms of treatment effectiveness.

There is a marginal benefit in terms of compliance, convenience and lower acquired drug resistance may be offset by unpredictable pharmacological properties of many FDC preparations. The choice of FDC or separate administration of ATT should be individualized rather than empiric.

Recently a study at TB sanatorium regarding risk factors for MDR-TB in adults has found that default of initial treatment is a major contributor to the risk of TB recurrence and thereby development of MDR - TB.

In our study we have found that treatment with fixed dose combination of ATT using patient wise under RNTCP is efficacious in both

.

pulmonary TB and also in TB adenitis. Moreover there was no difficulty in procurement of these drugs, had very good compliance, and fewer adverse effects.

In our study a correlation between the weight gain and treatment outcome was analysed. The results showed that there was a significant correlation between outcome and weight gain (0.979) in TB adenitis and (0.992) in case of pulmonary tuberculosis.

We also analysed the correlation between rise in hemoglobin level and treatment outcome. It also showed a strong positive correlation (0.819) in children treated for TB adenitis and also in children treated for pulmonary tuberculosis (0.829).

Weight gain and rise in hemoglobin level may be considered as one of the important indicators of good treatment outcome. Further studies may be required to confirm this correlation between rise in hemoglobin level and treatment outcome.

.

CONCLUSION

The following conclusions are arrived from this study.

1. The DOTS therapy using pediatric patient wise boxes under RNTCP is highly efficacious in childhood tuberculosis both in pulmonary and in TB adenitis.
2. There are no major adverse effects associated with these fixed drug formulations of patient wise boxes.
3. Malnutrition and anemia are more commonly associated with childhood tuberculosis both pulmonary and TB adenitis.
4. Weight gain and rise in hemoglobin have a strong positive correlation with treatment outcome in both TB adenitis and pulmonary tuberculosis
5. Weight gain and rise in hemoglobin level may be considered as one of the important indicators of good treatment outcome.

The compliance of drug intake in these children was very good and had no difficulty in procurement of these drugs. There were fewer side effects. The school attendance and performance was not affected significantly.

This good treatment outcome could be associated with the proper education about the disease and the treatment by the health care

.

professionals and to adherence of the therapy. This will in a large way help us in prevention of MDR-TB in children.

Thus more number of volunteers, health care workers, NGO's, private practioners should be encouraged to participate in the successful implementation of this programme in the community.

.

MASTER CHART TB ADENITIS

s.no	Name	Age	Sex	W1	W2	mal	cont	FNAC 1	FNAC 2	X-ray 1	X-ray 2	Hb 1	Hb 2	LFT 1	LFT 2	adv
1	Bala chander	1	m	7	8.5	yes	no	positive	negative	N	N	11.2	12.5	N	N	N
2	sri kalyan	2	m	8	10	yes	yes	positive	negative	abn	N	7	10.8	N	N	N
3	sakthi priya	10	f	30	34	no	yes	positive	positive	N	N	10.8	11.8	N	N	N
4	raghuram	11	m	32	34	no	no	positive	negative	N	N	11	12.5	N	N	N
5	krithika	11	f	26	28	yes	yes	positive	negative	abn	N	10.4	12	N	N	N
6	dhanushi	2	f	7	8	yes	yes	positive	negative	N	N	9.8	11.2	N	N	N
7	monish	9	m	26	29	no	no	positive	negative	N	N	8.8	10.6	N	N	N
8	dinesh	9	m	16	20	yes	no	positive	negative	N	N	11	12.5	N	N	Y
9	manikandan	8	m	15	19	yes	yes	positive	negative	N	N	10.8	12.8	N	N	N
10	sakshi	3	f	8	10	yes	yes	positive	negative	N	N	11.2	13	N	N	N
11	sivakumar	7	m	20	22	no	no	positive	negative	abn	N	12.4	12.8	N	N	Y
12	dilli babu	3	m	8	12	yes	no	positive	negative	N	N	10.8	11.8	N	N	N
13	pushpa rani	3	f	7	10	yes	no	positive	negative	N	N	12.4	13	N	N	N
14	santosh	5	m	12	14	yes	no	positive	negative	N	N	11.2	12.8	N	N	N
15	manikandan	10	m	22	25	yes	no	positive	positive	abn	N	12.8	12.5	N	N	Y
16	dharan	10	m	24	27	yes	no	positive	negative	N	N	12.4	12.9	N	N	N
17	pavithra	2	f	8	10	yes	yes	positive	negative	N	N	10.8	12.2	N	N	N
18	arul raj	5	m	12	16	yes	yes	positive	negative	abn	N	8.6	11.2	N	N	N
19	sooriya	12	m	36	37	no	no	positive	negative	N	N	9	11.4	N	N	Y
20	yugendran	2	m	8	10	yes	no	positive	negative	N	N	9.8	10.6	N	N	N
21	gokul	8	m	15	20	yes	no	positive	negative	N	N	9.6	12.5	N	N	N
22	samuel	2	m	8	10	yes	yes	positive	negative	N	N	10.2	11.6	N	N	N
23	pasupathy	2	m	7	9	yes	no	positive	negative	abn	N	12.4	13.4	N	N	N
24	kishore	10	m	20	24	yes	no	positive	negative	N	N	10.8	12.5	N	E	Y
25	siva	7	m	20	22	no	no	positive	negative	N	N	12.8	13.5	N	N	N
26	jeyasri	1	f	7	9	yes	yes	positive	negative	abn	N	10.6	11.6	N	N	N
27	priyadarshini	8	f	22	25	no	yes	positive	negative	N	N	8.6	9.6	N	N	N
28	hemalatha	3	f	10	13	yes	yes	positive	negative	N	N	9.8	10.2	N	N	N

29	yona	8	f	18	22	yes	no	positive	negative	N	N	10	10.8	N	N	Y
30	mahalakshmi	12	f	26	28	yes	no	positive	negative	N	N	10.2	11.4	N	N	N
31	saravanan	4	m	12	15	yes	no	positive	negative	N	N	11.2	11.8	N	E	N
32	prabhavathy	2	f	10	12	no	yes	positive	negative	abn	N	11.4	12.4	N	N	N
33	jayaprasad	6	f	14	17	yes	yes	positive	negative	N	N	10.2	12.6	N	E	N
34	karthik	3	m	9	12	yes	no	positive	negative	N	N	9.8	10.5	N	N	N
35	sandhiya uma	8	f	18	23	yes	no	positive	negative	N	N	9.6	11.2	N	E	Y
36	maheshwari	3	f	8	12	yes	yes	positive	negative	N	N	10.4	12.6	N	N	N
37	vetriselvi	12	f	36	38	no	no	positive	negative	N	N	10.8	12.8	N	N	N
38	aakash	8	m	22	25	no	yes	positive	negative	N	N	12.2	12.8	N	N	N
39	ashwini	3	m	8	11	yes	yes	positive	negative	N	N	12.8	12.8	N	N	N
40	manoj	2	m	7	10	yes	no	positive	negative	abn	N	10.8	11.2	N	N	N
41	anbalagan	12	m	24	27	yes	no	positive	negative	N	N	12.8	13.5	N	N	Y
42	santhiya	12	f	26	28	yes	yes	positive	negative	N	N	8.8	10.4	N	N	N
43	govindammal	4	m	10	14	yes	no	positive	negative	N	N	9.6	10.2	N	E	N
44	jennifer	12	m	28	32	yes	yes	positive	negative	abn	N	10.4	11.2	N	E	N
45	satish kumar	6	m	18	20	no	no	positive	negative	abn	N	11.2	12	N	N	Y
46	vignesh	10	m	20	24	yes	no	positive	negative	N	N	12.6	12.5	N	N	N
47	zubeida	10	f	22	26	yes	no	positive	negative	N	N	12	12.5	N	N	Y
48	manjula	7	m	20	22	no	yes	positive	negative	N	N	11	12	N	N	N
49	kamal	4	m	12	27	yes	no	positive	negative	N	N	9.2	9.8	N	N	N
50	nirmala	9	f	18	21	yes	no	positive	negative	abn	N	9.8	10.2	N	N	N
51	surendar	12	m	28	32	yes	no	positive	negative	N	N	12.4	13.5	N	N	N
52	ilavarasan	12	m	26	29	yes	no	positive	negative	N	N	10.4	11	N	N	N
53	vijay	8	m	18	22	yes	no	positive	negative	N	N	10.8	11.8	N	N	N
54	dhanalakshmi	12	f	30	31	yes	no	positive	negative	N	N	8.8	10.2	N	N	N
55	tamilarasan	2	m	8	11	yes	yes	positive	negative	N	N	7.8	10.4	N	N	N
56	vignesh	6	m	18	20	yes	no	positive	negative	N	N	12.8	13	N	N	N
57	deepa	12	f	35	38	no	no	positive	negative	N	N	12	12.5	N	N	N
58	suganthi	5	f	12	14	yes	no	positive	negative	abn	N	11.2	11.4	N	N	N
59	swetha	9	f	20	23	yes	no	positive	negative	N	N	9.6	10.2	N	N	N
60	elizabeth	12	f	34	36	no	no	positive	negative	N	N	9.8	11	N	N	N

61	jennifer	5	f	13	15	yes	yes	positive	negative	N	N	10.4	11.2	N	N	N
62	barath kumar	11	m	25	27	yes	no	positive	negative	abn	N	11	12.4	N	E	Y
63	prakash	12	m	29	31	yes	no	positive	negative	N	N	11.4	12.5	N	N	N
64	ramapriya	11	f	27	30	yes	no	positive	negative	N	N	12	13.5	N	N	N
65	sushmitha	3	f	14	17	no	yes	positive	negative	N	N	12.8	13	N	N	N
66	manikandan	11	m	25	28	yes	no	positive	negative	N	N	9.8	10.8	N	N	N
67	suriya	2	m	7	10	yes	yes	positive	negative	abn	N	9.6	10.2	N	N	Y
68	stella	11	m	32	34	no	no	positive	negative	N	N	10.2	10.4	N	N	N
69	deepa	9	f	19	22	yes	no	positive	negative	N	N	11.2	11.8	N	N	N
70	lavanya	11	f	25	28	yes	no	positive	negative	N	N	12.4	12.5	N	N	N
71	janani	8	f	24	25	no	yes	positive	negative	N	N	10.2	11	N	N	N
72	gayathri	9	f	18	19	yes	yes	positive	negative	N	N	12.2	12.4	N	N	N
73	kalyani	12	f	25	29	yes	no	positive	negative	abn	N	9.8	10.6	N	N	N
74	nivetha	9	f	18	22	yes	yes	positive	negative	N	N	9.6	11.4	N	N	N
75	preethika	7	f	16	20	yes	no	positive	negative	N	N	11	12	N	N	N
76	mohan	5	m	15	19	no	no	positive	negative	abn	N	10.6	12.4	N	N	N
77	amuldoss	5	m	12	15	yes	yes	positive	negative	N	N	11.8	12.8	N	N	N
78	vignesh	3	m	8	12	yes	yes	positive	negative	N	N	12.4	12.5	N	N	N
79	santosh	3	m	10	12	yes	yes	positive	negative	abn	N	12	12.8	N	N	N
80	jhansi	8	f	17	22	yes	no	positive	negative	N	N	10.6	12.2	N	N	N
81	karthik	9	m	22	24	yes	no	positive	negative	abn	N	9.4	10.6	N	N	N
82	gayathri	5	f	17	18	no	yes	positive	negative	N	N	10.4	11.2	N	N	N

MASTER CHART- PULMONARY TB

	Name	Age	Sex	W 1	W 2	mal	cont	mantoux	AFB 1	AFB 2	X-ray chest 1	X-ray chest 2	Hb 1	Hb 2	LFT 1	LFT 2	adverse symptoms
1	nivetha	8	f	18	21	yes	yes	negative	negative		abnormal	normal	10.2	11.2	N	N	N
2	sakthivel	12	m	32	34	no	no	negative	negative		abnormal	normal	11	12.4	N	N	N
3	praveen	2	m	8	11	yes	no	positive	negative		abnormal	normal	10.2	12.8	N	N	Y
4	revathy	8	f	14	15	yes	no	positive	negative		abnormal	normal	10.6	13.2	N	N	N
5	nithya sri	9	f	18	19	yes	yes	negative	negative		abnormal	normal	11.2	12.8	N	N	N
6	esthar	6	f	13	15	yes	no	positive	negative		abnormal	normal	12.8	13.2	N	N	N
7	sonya	12	f	28	32	yes	yes	positive	positive	negative	abnormal	normal	11.2	11.8	N	N	N
8	ramarao	8	m	16	20	yes	No	positive	positive	negative	abnormal	normal	12.6	12.8	N	N	N
9	maheshwari	10	f	22	25	yes	yes	negative	negative		abnormal	normal	8.4	10.6	N	E	N
10	harish kumar	5	m	15	18	yes	no	negative	negative		abnormal	normal	8.8	9.8	N	N	Y
11	yuvasree	12	f	23	24	yes	yes	positive	positive	negative	abnormal	normal	11.2	12.5	N	N	N
12	venkat	1	m	7	9	yes	yes	negative	negative		abnormal	normal	9.8	11	N	N	N
13	sriji	12	f	27	30	yes	yes	negative	negative		abnormal	normal	10.6	11.5	N	N	N
14	tamini	2	m	8	9	yes	no	negative	negative		abnormal	normal	11.4	12.4	N	N	N
15	karthiga	2	m	8	10	yes	no	positive	negative		abnormal	normal	10	11.4	N	N	Y
16	meena	12	f	25	26	yes	yes	positive	negative		abnormal	normal	12.6	12.5	N	N	N
17	shaheen	7	f	16	18	yes	no	negative	negative		abnormal	normal	12.8	13.1	N	N	Y
18	madhan kumar	4	m	12	13	yes	yes	negative	negative		abnormal	normal	10.6	11.4	N	N	N
19	manish	9	m	16	19	yes	yes	negative	positive	negative	abnormal	normal	10.6	12.5	N	N	N
20	priya	6	f	13	15	no	no	negative	negative		abnormal	normal	11.6	12	N	N	N
21	ashok	6	m	15	17	yes	yes	negative	negative		abnormal	normal	9.8	11	N	N	N
22	harish kumar	5	m	15	18	yes	no	negative	negative		abnormal	normal	8.8	9.8	N	N	Y
23	yuvasree	12	f	23	24	yes	yes	positive	negative		abnormal	normal	11.2	12.5	N	N	N
24	venkat	1	m	7	9	yes	yes	negative	negative		abnormal	normal	9.8	11	N	N	N
25	sriji	12	f	27	30	yes	yes	negative	negative		abnormal	normal	10.6	11.5	N	N	N
26	tamini	2	m	8	9	yes	no	negative	negative		abnormal	normal	11.4	12.4	N	N	N
27	karthiga	2	m	8	10	yes	no	positive	negative		abnormal	normal	10	11.4	N	N	Y

28	meena	12	f	25	26	yes	yes	positive	negative		abnormal	normal	12.6	12.5	N	N	N
29	shaheen	7	f	16	18	yes	no	negative	negative		abnormal	normal	12.8	13.1	N	N	Y
30	manish	9	m	16	19	yes	yes	negative	positive	negative	abnormal	normal	10.6	12.5	N	N	N

PROFORMA

S. No. **NAME** **AGE** **SEX**

SOCIOECONOMIC CLASS

HISTORY Yes / No DURATION

1. Cough ?
2. Fever ?
3. Swelling in the neck ?
4. Failure to gan Wt / Loss of Wt?
5. Loss of appetite ?

H / O Contact with Open case of TB? Yes / No

Any past H / O Tuberculosis? Yes / No

Category

Treatment completed ? Yes / No

BCG Status ? Yes / No

Weight Height MAC

Nutritional status

INVESTIGATIONS:

Mantoux

Sputum / RGJ for AFB 1)

2)

3)

FNAC

X-ray Chest

CT / MRI Chest

ESR

LFT Sr. Billirubin

SGOT

SGPT

Alkaline Phosphatase

Sr Uric acid

Blood urea

Sr. Creatinine

Hb %

Tc

Dc

Platelets

P/S

HIV Status

Parentral screening

DIAGNOSIS:

TREATMENT:

Category :

Started on :

Completed on :

PWB used

FOLLOW UP:

Weight

Height

MAC

Nutritional status

INVESTIGATIONS:

Sputum / RGJ for AFB 1)

2)

3)

FNAC

X-ray Chest

CT / MRI Chest

ESR

LFT Sr. Billirubin

SGOT

SGPT

Alkaline Phosphatase

Sr Uric acid

Blood urea

Sr. Creatinine

Hb %

Tc

Dc

Platelets

BIBLIOGRAPHY

1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project.JAMA. 1999; 82:67786.
2. Nelson LJ, Wells CD, Global epidemiology of childhood tuberculosis. Int. J Tuberc Lung Dis 2004;8(5):636–647.
3. Guidance for national tuberculosis programmes on the management of tuberculosis in children: World Health Organization. Available at: WHO/HTM/TB/2006.371. The Pediatric Infectious Disease Journal. 21(2):91-97, February 2002.
4. Kochi A. The global tuberculosis situation and the new control strategy of the World Health Organisation. *Tubercle* 1991; **72**: 1.
5. World Health Organisation (WHO). WHO report on the Tuberculosis epidemic. Geneva: *WHO*; 1996.
6. WHO. Treatment of tuberculosis. Guidelines for National Programmes. Geneva; WHO; 2003 (WHO/CDS/TB 2003.313).
7. Central TB Division (CTD), DGHS, MoHFW, Government of India. TB India 2003: RNTCP Status Report. Delhi: CTD; 2003.
8. www.tbcindia.org Accessed 7th October 2003.

9. Chakraborty AK. Prevalence and incidence of tuberculosis infection and disease in India. Geneva: WHO; 1997 *(WHO/ TB/97*.231).
10. Gie R. Diagnostic atlas of intrathoracic tuberculosis in children: a guide for low income countries.
11. Paris, International Union Against Tuberculosis and Lung Disease, 2003.
12. Crofton J, Horn N, Miller F. Clinical tuberculosis, 2nd ed. London, MacMillan Press, 1999.
13. Management of tuberculosis: a guide for low income countries, 5th ed. Paris, International Union
14. Against Tuberculosis and Lung Disease, 2005. *TB/HIV: a clinical manual*, 2nd ed. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.329).
15. Treatment of tuberculosis: guidelines for national programmes, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/ 2003.313).
16. Ileana Puiu, Jurnalul Pediatrului – Year X, Vol. X, Nr. 39-40, July December 2007.
17. Castro DJ, Hoover L, et all. Cervical mycobacterial limphadenitis. Arch. Otolaryngol 1985; 111: 816 - 9.

18. Dandapat MC, Mishra BM, Dash SP, et al. Peripheral lymph node tuberculosis: a review of 80 cases. *Br J Surg* 1990; 77: 911 - 912.
19. Jhaa BC, Dass A, et al. Cervical tuberculous lymphadenopathy: changing clinical pattern and concepts in management. *Postgrad Med J*, 2001; 77: 185 - 7.
20. Polesky A, Grove W, Bhatia G. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. Medicina (Baltimore). 2005 Nov; 84(6):350- 62.
21. Lodha R, Kabra S K, Seth V. Diagnosis of tuberculosis. Indian J Pediatr 2000; 67(supplement): S3-S8.
22. Treatment of childhood tuberculosis: Consensus Statement Recommendations of Indian Academy of Pediatrics. Indian Pediatr 1997; 34: 1093-1096
23. Verma K, Kapila K. Aspiration cytology for the diagnosis of tuberculosis perspective in India. Indian J Pediatr 2002; 69 (supplement): S39- S43.
24. Seth V, Kabra SK, Lodha R. Management of tuberculosis. In Essentials of Tuberculosis in Children 2nd Edition, Eds Seth V and Kabra SK. Delhi Jaypee Brothers, 2001, pp 349-354.

25. Al-Dossary FS, Ong LT, Correa AG, Starke JR. Treatment of childhood tuberculosis with a six month directly observed regimen of only two weeks of daily therapy. Pediatr Infect Dis J 2002; 21: 91-97.
26. Biddulph J. Short course chemotherapy for childhood tuberculosis. Pediatr Infect Dis J 1990; 9: 794-801
27. Jawahar MS, Sivasubramanian S, Vijayan VK, Ramakrishnan CV, Paramasivan CN, Selvakumar V, *et al*. Short course chemotherapy for tuberculous lymphadenitis in children. BMJ 1990; 301:359-362.
28. Kumar L, Dhand R, Singhi PD, Rao KL, Katariya S. A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. Pediatr Infect Dis J 1990; 9: 802-806.
29. Biddulph J. Short course chemotherapy forchildhood tuberculosis. Pediatr Infect Dis J 1990; 9: 794-801.
30. Jawahar MS, Sivasubramanian S, Vijayan VK, Ramakrishnan CV, Paramasivan CN, Selvakumar V, *et al*. Short course chemotherapy for tuberculous lymphadenitis in children. BMJ 1990; 301:359-362.
31. Van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der MeerJW.Tuberculous meningitis: is a 6-month treatment regimen sufficient? Int J Tuberc Lung Dis 2001; 5: 1028-1035.

32. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis 1998; 2: 704-711.
33. Jacobs RF, Sunakorn P, Chotpitayasunonah T, Pope S, Kelleher K. Intensive short course chemotherapy for tuberculous meningitis. Pediatr Infect Dis J 1992; 11: 194-198.
34. Ohkawa K, Hashiguchi M, Ohno K, Kiuchi C, Takahashi S, Kondo S, *et al*. Risk factors for antituberculous chemotherapy-induced hepatotoxicity in Japanese pediatric patients. Clin Pharmacol Ther 2002; 72: 220-226.
35. D vijayasekaran et al Mantoux and Contact Positivity in Tuberculosis. Indian journal of Pediatrics 2006; 73:989-993
36. Balaji et al Fine Needle Aspiration Cytology in Childhood TB lymphadenitis. Indian journal of Pediatrics 2009; 72:973-977
37. RNTCP Status Report. TB India 2007. Central TB Division, DGHS, MoHFW. New Delhi: Government of India; 2007. p. 40- 42.
38. Center for Disease Control. Adverse drug reaction among children treated for tuberculosis. MMWR 1980; 29: 589-591.
39. Nelson Text Book of Pediatrics tuberculosis chapter,18th edition, p.1240-1245,

40. Te Water Naude JM, Donald PR, Hussey GD, Kibel MA, Louw A, Perkins DR, *et al*. Twice weekly *vs* daily chemotherapy for childhood tuberculosis. Pediatr Infect Dis 2000; 19: 405-410.
41. CK Indhumathi et al,Intermittent Short Course Therapy for Tuberculosis. Indian Pediatrics 2009; October 14, e-pub ahead of print.
42. Tsakilidis D, et al., Pediatr Infect Dis J 1992; 22:432-438.
43. Göçmen A, Ozçelic U, Kiper N, Toppare M, Kaya S, Cengizlier R, *et al*. Short course intermittent chemotherapy in childhood tuberculosis. Infection 1993; 21: 324-327.
44. Joseph L Mathew Fixed-Dose Drug Combination for Treatment of Tuberculosis , Indian Pediatrics; 2009;43:877-880.